Surgical adhesions can be treated, prevented in mice

By Krista Conger

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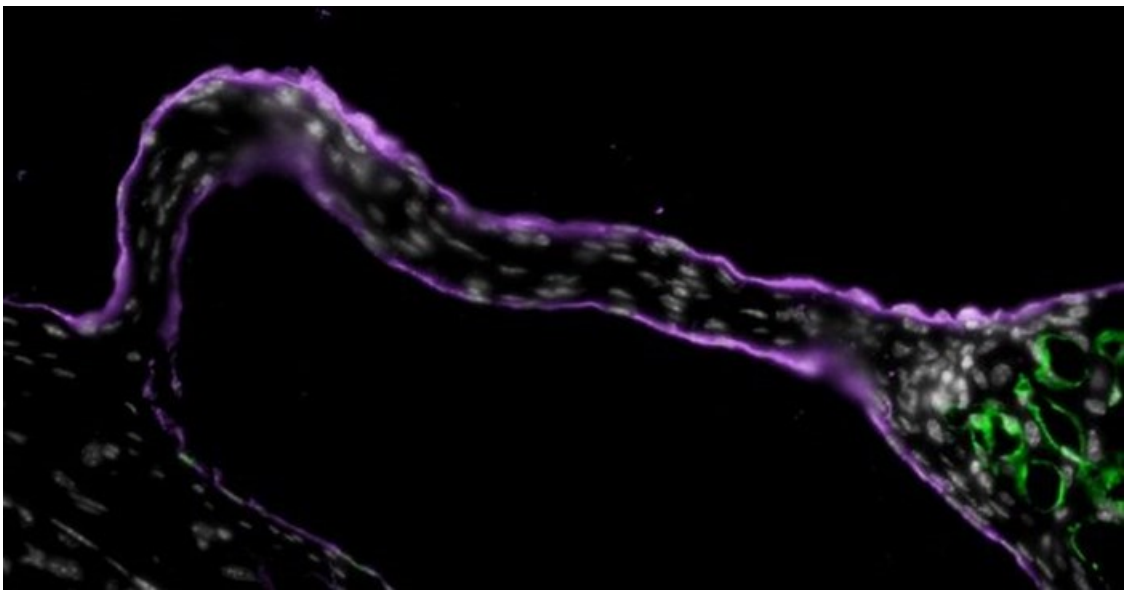
A cellular culprit - as well as a possible treatment - for a common, sometimes life-threatening post-surgical complication has been identified by researchers at the Stanford University School of Medicine.



An image of a string adhesion between the liver and the intestine. The cell nuclei are stained white.

Jonathan Tsai

The condition arises when abnormal fibrous connections called adhesions form after abdominal surgery, tethering the normally slippery organs together or anchoring them to the abdominal wall. Symptoms can include chronic pain, female infertility, bowel obstruction and, occasionally, death. According to the National Institutes of Health, the annual cost of treating post-surgical adhesions in the United States surpasses $1bn.

“This is a very common surgical complication, but it’s not been well-studied,” said Dr Jonathan Tsai, a former medical student at Stanford and now resident physician at Brigham and Women’s Hospital in Boston. “Until now, it wasn’t even known what cell type was involved in originating the adhesions. Now we’ve come up with a way to isolate the injured tissue before they form the adhesions, and identify the molecular pathways involved.”

The researchers developed and studied a mouse model of adhesion formation to identify the cell responsible for the initial steps. They also showed that an antibody-based therapy could break down those that had already formed. The hope is that

similar techniques could help treat post-surgical adhesions in humans.

The researchers found that a combination of two antibodies — one that targets the cells responsible for adhesion formation and another that silences a “don’t eat me” signal that cancer cells use to evade the immune system — could significantly reduce the severity of established adhesions in the animals.

A common complication

When the mesothelium that lines the abdominal cavity is disturbed, fibrous connections form between neighbouring surfaces, ranging in severity from single threads to vast, immobilising webs. The NIH estimates that about 93% of abdominal surgeries result in adhesions and that about 20% of surgical patients will be re-hospitalised for adhesion-related complications.

Although the complication is common, it’s not well-understood. Researchers have identified some cell types involved in later steps of the process, but it’s not been known which cell type is responsible for the initial steps. It appears to arise in regions where blood flow is restricted, such as in the tiny pinches of tissue caused by surgical sutures, leading to hypoxia in the region.

Tsai used a mouse model of the condition to trace the formation of adhesions and the resulting patterns of gene expression in the mesothelium.

“We found that adhesions arise from cells of the mesothelium after injury,” Tsai said. “By tracing the patterns of gene expression, we were able to come up with a cellular ‘family tree’ for these fibrotic tissues and identify the biological pathways involved.”

Tsai and his colleagues found that, in mice, cells of the mesothelium respond to hypoxia by making a protein called HIF1alpha. This in turn promotes the expression of other proteins essential for the formation of adhesions. When the researchers treated the animals with a small molecule that inhibited the activity of HIF1alpha, the resulting adhesions were significantly less severe.

Possible role for macrophages

They also found that treating the animals with antibodies that bind to mesothelin, a protein specific to injured mesothelium, significantly reduced the severity of adhesions that had already formed. Combining anti-mesothelin antibodies with an anti-CD47 antibody had an even greater effect, suggesting that roving immune cells called macrophages, which gobble up sick or dying cells, may also play a role in removing abnormal fibrous tissue.

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When the mesothelium is irritated, it begins to express mesothelin, which is normally expressed only very early in development. This triggers proliferation of the cells and initiates an inflammatory cascade that brings in immune cells and proteins that glom everything up with fibrous tissue. But these cells also have CD47 on their surface, and we’ve found that anti-CD47 can synergise with anti-mesothelin to remove these adhesions after they’ve been formed.

Finally, the researchers studied samples of adhesions that had been removed from patients. They found that the human tissue expressed many of the same genes and used similar biological pathways as those the researchers identified in the mice. Tsai and his colleagues are hopeful that similar antibody-based treatments may help prevent or treat the formation of adhesions in people.

Source: Stanford University School of Medicine